UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,411	04/11/2002	Paul Simmons	A20-033	9003

7590 06/28/2005

EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	

R. Neil Sudo/Henry D. Coleman
William J Sapone
Coleman Sudol Sapone
714 Colorado Avenue
Bridgeport, CT 06605-1601

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,411	SIMMONS ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28,31,34,40-45 and 47-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28,31,34,40-45 and 47-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/02/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to comply with Sequence requirements.

DETAILED ACTION

1. Applicant's amendment, filed 05/11/2005 is acknowledged.

Claims 25-28,31,34, 40-45, 47-58 are pending.

Applicant's election with traverse of Group II, claims 25-28,31, 34, 40-45, 47-51, now claims 25-28,31,34, 40-45, 47-58 and STRO-1 as a specific surface markers expressed on mesenchymal precursor cells in the reply filed on 05/11/05 is acknowledged. The traversal is on the ground that it would be no undue burden to examine all species of surface markers expressed on mesenchymal precursor cells.

Upon consideration of applicant's arguments, the prior art search has been extended to include all species of surface markers expressed on mesenchymal precursor cells. The species election is hereby withdrawn.

Claims 25-28, 31, 34, 40-45 and 47-58 read on an enriched cell population, wherein at least 1% of the cells carry at least two markers specific for mesenchymal precursor cells, wherein said marker are recited in claim 26 under consideration in the instant application.

2. This application contains sequences disclosures on page 22, lines 24 and 25 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Applicant is reminded to amend the specification and the claims accordingly.

3. The disclosure is objected to because of the following: the specification on page 6, line 34 disclosed that the reagents suitable for use in labeling surface markers can be found in Table 4. There is no Table 4 in the specification as originally filed.

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 26, 27 and 53- 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 26 is indefinite and ambiguous in the recitation of "6-19" , line 5, as a surface marker specific for mesenchymal precursor cells. The characteristics and metes and bounds of the term "6-19" as a surface marker specific for mesenchymal precursor cells is unclear and indefinite.

B. Claims 26, 27 and 53-57 are indefinite and ambiguous in the recitation of "... antigen identified by STRO-1 and VCAM-1", or "... antigen identified by STRO-1" or "... antigen identified by VCAM-1" or "... antigen identified by THY-1" or "... antigen identified by CD146 " accordingly. It is unclear how one can identify antigen by the same antigen. It is noted that the Specification disclosed that STRO-1, VCAM-1, THY-1 and CD146 are surface markers specific for mesenchymal precursor cells that can be identified by **antibodies** that are specific to said markers. It is unclear if Applicant means that: (i) antigen **identified as** STRO-1, VCAM-1 etc. antigen; or (ii) antigen **identified by** agent that can specifically binds to said antigen, for example by antibody specific for STRO-1, VCAM-1 etc. It is suggested that said claims be amended to clarify this issue.

C. Claim 58 is indefinite and ambiguous in the recitation of " ... wherein the STRO-1 ^{bright} cells.. ". There is insufficient antecedent basis for this limitation in the claim, since the base Claim 25 does not recite "STRO-1 ^{bright} cells".

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 26, 52 and 56-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

(i) "...surface markers specific for mesenchymal precursor cells consisting of integrin beta, STRO-2, CD146 or any combination thereof" claimed in claim 26; (ii) " ...cells that are positive for one or more markers selected from the group consisting of $CD146^{bright}$ and STRO-2 ^{bright}", claimed in claim 52; (iii) "an enriched cell population as in claim 52 wherein the $CD146^{bright}$ cells carry a high copy number of an antigen identified by CD146" claimed in claim 56; (iv) "an enriched cell population as in claim 52 wherein the STRO-2 ^{bright} cells carry a high copy number of an antigen identified by STRO-2 " claimed in claim 57; (v) "an enriched cell population as in claim 25 wherein Stro-1 ^{bright} cells are negative for at least one marker selected from the group consisting of CBFA-1, collagen type II, PPARγ2 and glycophorin A" claimed in claim 58 represent a departure from the specification and the claims as originally filed and applicant has not pointed out where the support comes from.

The specification and the claims as originally field only support the group of surface markers specific for mesenchymal precursor cells consisting of the group as recited in the Specification on page 6, lines 30-33 and originally recited in claim 26.

9. Claims 25-28, 31, 34, 40-45 and 47-51 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enriched cell population wherein at least 1% of the cells are mesenchymal precursor cells capable of giving rise to colony forming units-fibroblasr (CFU-F) does not reasonably provide enablement for: (i) an enriched cell population wherein at least 1% of *any* cells capable of giving rise to colony forming units-fibroblasr (CFU-F), claimed in claims 25-28,31, 34, 40-44 and 58, or (ii) a composition including said cells, claimed in claims 45, 47-51. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The claims as written encompass the genus of *any* cells that are capable of giving rise to CFU-F.

Applicant discloses only an enriched population of cells that are mesenchymal precursor cells that are capable of giving rise to CFU-F (see Examples on overlapping pages 18-20 in particular). Applicant also disclosed that only bone marrow multi-potential mesenchymal precursor cell , **not any cells** , can be readily measured by their ability to form CFU-F in short term liquid culture (see page 3, lines 1-10 in particular). Applicant has not taught how to make and/or use an enriched cell population wherein at least 1% of *any* cells capable of giving rise to colony forming units-fibroblast (CFU-F). The structural characteristics of *any* cells are not defined in the Specification. Moreover, Gronthos et al., (J of Cell Science 2003, V.116, pages 1827-1835) teach that various stromal cell types have different proliferative potential, considerable heterogeneous in terms of size, morphology, histochemistry and developmental potential and that in a number of species, including human, putative subset of cells i.e. mesenchymal precursor cells have been identified by their ability to form colonies of cells morphologically resembling fibroblast. Said clonogenic progenitor responsible for colony formation is referred as CFU-F (see entire document, page 1827 in particular).

Since the instant fact pattern fails to indicate that representative number of structurally related cells, capable of giving rise to CFU-F is disclosed, the artisan would not know the identity of a reasonable number of representative cells falling within the scope of the instant claims and consequently would not know how to make them.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed (i) an enriched cell population wherein at least 1% of *any* cells capable of giving rise to colony forming units-fibroblast (CFU-F), claimed in claims 25-28,31, 34, 40-44 and 58, or (ii) a composition including said cells, claimed in claims 45, 47-51 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the

scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.
10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

11. Claims 25-28, 31, 34, 40, 41, 44, 48, 49 and 52-58 are rejected under 35 U.S.C. 102(b) as being anticipated by Simmons et al (IDS).

Simmonst et al., teach an enriched cell population of mesenchymal precursors cells that are capable of giving rise to CFU-F and composition comprising said cells (see entire document, page 272 and Fig.2 in particular). Simmonst et al., teach that said enriched cell population carry the antigen identified by STRO-1 antibody and that said cells are also positive for VCAM, LFA-3, THY-1, P-selectin, L-selectin, CD49b/CD29 surface markers (see Table 1 in particular). Simmonst et al., teach that said cells are capable of differentiation into at least adipocytes, osteoblasts and fibroblast (see Fig.1 in particular). Although the reference is silent about that said enriched cell population of mesenchymal precursors comprises at least 1%, 5%, 10% or 40 % of cells capable of giving rise to CFU-F, as recited in claims 25-28, 31and 34 or that composition comprising said cells also includes hemopoietic cells, as claimed in claim 49, or that said cell population are positive for CD146 or STRO-2, as claimed in claims 56 and 57 ; or that SRTO-1 ^{bright} cells are negative for at least one marker as recited in claim 58, these limitation would be inherent properties of the referenced cell composition because the referenced cell composition was obtained by the same method as claimed. Since the office does not have a laboratory to test the reference enriched cell population, it is applicant's burden to show that the reference cell population does not have the same properties as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

Claims 41, 44 , 48 and 49 are included because the claimed functional limitation would be inherent properties of the referenced enriched cell population and composition comprising said cells. A cell population and composition comprising said cells is cell population and composition comprising said cells irrespective of their intended use in the absence of evidence of structural difference.

The reference teaching anticipates the claimed invention.

12. Claims 25-28, 31, 34, 40, 41, 44, 47, 48, 49 and 52-58 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,087,113 as is evidenced by Simmons et al (IDS) and the disclosure of the instant Specification on page 16, lines 20-30.

US Patent '113 teaches an enriched cell population of mesenchymal precursors cells and a composition comprising said cells. (see entire document, overlapping columns 3 and 4 in particular). US Patent '113 teaches that it is possible to get up to 95% of enriched cell population of mesenchymal precursors cells (see column 7, lines 10-25 in particular). US Patent '113 teaches that said enriched cell population carry the antigen identified by STRO-1 antibody (see column 40, lines 21-35 in particular). US Patent '113 teaches that said cells are capable of differentiation into cartilaginous and fibrous tissue (see overlapping columns 8 and 9 in particular). US Patent '113 teaches a composition wherein the mesenchymal precursor cells are preadsorbed onto ceramic vehicles that are suitable for implantation to augment bone marrow transplantation (see column 9, lines 8-15, column 14, lines 15-25 and Example 7 in particular). Although the reference is silent that ceramic vehicles were precoated with fibronectin, it is noted that US Patent '113 teaches that said ceramic vehicles were pretreated as previously disclosed, by referenced to the inventors previous publication by Caplan et al (see column 14, lines 12-30) . As disclosed in the instant Specification on page 16, lines 20-30, the ceramic vehicles were pre-treated with fibronectin as reported by Caplan et al. Thus ceramic vehicles disclosed by US Patent '113 would be inherently precoated by the same method as recited in the instant claim, i.e. with fibronectin. Although the reference is silent that said enriched cell population of mesenchymal precursors are capable of giving rise to CFU-F, as recited in claims 25, or carry at least two markers specific for mesenchymal precursor cells as recited in claim 26, these limitation would be inherent properties of the referenced cell composition as is evidenced by Simmons et al (IDS). Simmons et al., teach the ability to give rise to CFU-F is an inherent property of mesenchymal precursors cells (see page 272 in particular). Simmonst et al., further teach that cells that carry the antigen identified by STRO-1 antibody are also positive for markers specific for mesenchymal precursor cells such as VCAM, LFA-3, THY-1, P-selectin, L-selectin, CD49b/CD29 surface markers (see Table 1 in particular). Moreover, although the reference is silent about the fact that the recited composition comprising mesenchymal precursors cells also includes hemopoietic cells, as claimed in claim 49, or that said cell population are positive for CD146 or STRO-2, as claimed in claims 56 and 57 ; or that SRTO-1 ^{bright} cells are negative for at least one marker as recited in claim 58, these limitation would be inherent properties of the referenced cell composition because the referenced cell composition was obtained by the same method as claimed. Since the office does not have a laboratory to test the reference enriched cell population, it is applicant's burden to show that the reference cell population does not have the same properties as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

Claims 41, 44 , 48 and 49 are included because the claimed functional limitation would be inherent properties of the referenced enriched cell population and composition comprising said cells. A cell population and composition comprising said cells are cell population and composition comprising said cells irrespective of their intended use in the absence of evidence of structural difference.

The reference teaching anticipates the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 25, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simmons et al (IDS) in view of US Patent 6,087113 as is evidenced by the disclosure of the instant Specification on page 16, lines 20-30.

The teaching Simmons et al., US Patent '113 and disclosure of the instant Specification has been discussed, supra.

The claimed invention differs from the reference teaching in that the Simmons et al., do not explicitly teach a composition comprising an enriched cell population of cells capable of giving rise to CFU-F, that are preadsorbed onto ceramic vehicles and are suitable for implantation to augment bone marrow transplantation, as claimed in claim 47.

Simmons et al., further teach that enriched population of progenitor cells capable of giving rise to CFU-F can be used in treatment various disorders of the hematopoietic system.

US Patent '113 teaches a composition wherein the mesenchymal precursor cells are preadsorbed onto ceramic vehicles that are suitable for implantation to augment bone marrow transplantation (see column 9, lines 8-15, column 14, lines 15-25 and Example 7 in particular). Although the reference is silent that ceramic vehicles were precoated with fibronectin, it is noted

that US Patent '113 teaches that said ceramic vehicles were pretreated as previously disclosed, by referenced to the inventors previous publication by Caplan et al (see column 14, lines 12-30) . As disclosed in the instant Specification on page 16, lines 20-30, the ceramic vehicles were pre-treated with fibronectin as reported by Caplan et al. Thus, ceramic vehicles disclosed by US Patent '113 would be inherently precoated by the same method as recited in the instant claim, i.e. with fibronectin.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '113 to those of Simmons et al., to obtain a claimed composition comprising an enriched cell population of cells capable of giving rise to CFU-F, that are preadsorbed onto ceramic vehicles and are suitable for implantation to augment bone marrow transplantation.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because a composition comprising a ceramic vehicles with preadsorbed mesenchymal progenitor cells can be used for correction or modifying connective tissue disorder or enhancing the implantation as taught by US Patent '113. The referenced cells taught by US Patent '113 by can be substitute by the cells taught by Simmons et al., to generate a composition comprising population of cells capable of giving rise to CFU-F, that are preadsorbed onto ceramic vehicles and are suitable for implantation . The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 25, 42, 43, 45, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simmons et al (IDS) or US Patent 6,087113 each in view of US Patent 5,591,625.

The teaching Simmons et al., and US Patent '113 has been discussed, supra.

Simmons et al further teach that mesenchymal precursors cells that are capable of giving rise to CFU-F are ideal target for gene therapy and may provide a means of treating disorders of the hemopoietic system (see page 278 in particular).

The claimed invention differs from the reference teaching in that Simmons et al., or US Patent 6,087113 does not explicitly teaches an enriched cells population wherein said cells are capable of giving rise to CFU-F or a composition comprising said cells wherein said cells has an exogenous nucleic acid transformed in to it, as claimed in claims 42 or 50 or wherein said cells has an exogenous nucleic acid that express a therapeutic agent transformed in to it, as claimed in claims 43 or 51 .

US Patent ' 625 teaches genetically engineered human mesenchymal stem and progenitor cells that have been transformed with exogenous nucleic acid that expresses a therapeutic agent (see entire document, overlapping column 1 and 2 in particular). US Patent' 625 teaches that said cells can be used to treat various diseases including genetic disorders, diseases of bone and cartilage and bone marrow or to be use to release of therapeutics (see column 2, lines 1-65 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '625 to those of Simmons et al., or US Patent '113 to obtain a claimed an enriched cells population wherein said cells are capable of giving rise to CFU-F or a composition comprising said cells wherein said cells has an exogenous nucleic acid transformed in to it or wherein said cells has an exogenous nucleic acid that express a therapeutic agent transformed in to it.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because a genetically engineered human mesenchymal stem and progenitor cells that have been transformed with exogenous nucleic acid that expresses a therapeutic agent can be used to treat various diseases including genetic disorders, diseases of bone and cartilage and bone marrow or to be use to release of therapeutics as taught by US Patent '625 . Said cells can be substituted by the cells taught by Simmons et al., or US Patent '113 because mesenchymal precursors cells that are capable of giving rise to CFU-F are ideal target for gene therapy and may provide a means of treating disorders of the hemopoietic system human mesenchymal progenitor cells that are used to treat diseases, for example of the hematopoietic system as taught by Simmons et al., or for repairing connective tissue damage, as taught by US Patent'113. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 25-28, 31, 34, 40, 41, 44, 48, 49 and 52-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1- 39 and 68- 78 of copending Application No. 10/813747. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1- 39 and 68- 78 of copending Application No. 10/813747 recited an enriches cell population of mesenchymal precursor cells, co-expressing STRO-1 and VCAM-1, wherein at least 1% of the cells capable of forming a clonogenic colony and are SRO-1 ^{bright} (see claims 6, 7, 25-30 and 68-74 in particular), or capable of differentiation into at least two commited cell types (see claims 31 and 75 in particular). Although the reference claims are silent about that said enriched cell population of mesenchymal precursors or composition comprising said cells also includes hemopoietic cells, as claimed in claim 49, or that said cell population are positive for CD146 or STRO-2, as claimed in claims 56 and 57 ; or that SRTO-1 ^{bright} cells are negative for at least one marker as recited in claim 58, these limitation would be inherent properties of the referenced cell composition because the referenced cell composition was obtained by the same method as claimed. Since the office does not have a laboratory to test the reference enriched cell population, it is applicant's burden to show that the reference cell population does not have the same properties as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

Claims 41, 44 , 48 and 49 are included because the claimed functional limitation would be inherent properties of the referenced enriched cell population and composition comprising said cells. A cell population and composition comprising said cells is cell population and composition comprising said cells irrespective of their intended use in the absence of evidence of structural difference.

This is a provisiónal obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 25, 45 and 47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1- 39 and 68- 78 of copending Application No. 10/813747 in view of US Patent 6,087113 as is evidenced by the disclosure of the instant Specification on page 16, lines 20-30 .

The teachings of claims 1- 39 and 68- 78 of copending Application No. 10/813747 has been discussed supra.

Claims 1- 39 and 68- 78 of copending Application No. 10/813747 do not explicitly recites a composition comprising an enriched cell population of cells capable of giving rise to CFU-F, that are preadsorbed onto ceramic vehicles and are suitable for implantation to augment bone marrow transplantation.

US Patent '113 teaches a composition wherein the mesenchymal precursor cells are preadsorbed onto ceramic vehicles that are suitable for implantation to augment bone marrow transplantation (see column 9, lines 8-15, column 14, lines 15-25 and Example 7 in particular). Although the reference is silent that ceramic vehicles were precoated with fibronectin, it is noted that US Patent '113 teaches that said ceramic vehicles were pretreated as previously disclosed, by referenced to the inventors previous publication by Caplan et al (see column 14, lines 12-30) . As is evidenced from the disclosure of the instant Specification on page 16, lines 20-30 the ceramic vehicles were pre-treated with fibronectin as reported by Caplan et al. Thus ceramic vehicles disclosed by US Patent '113 would be precoated with fibronectin.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '113 to those of claims 1- 39 and 68- 78 copending Application No. 10/813747 to obtain a claimed composition comprising an enriched cell population of cells capable of giving rise to CFU-F, that are preadsorbed onto ceramic vehicles and are suitable for implantation to augment bone marrow transplantation.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because a composition comprising a ceramic vehicles with preadsorbed mesenchymal progenitor cells can be used for correction or modifying connective tissue disorder or enhancing the implantation or as taught by US Patent '113. The referenced cells are the same cells as taught by claims 1- 39 and 68- 78 thus the cells taught by US Patent '113 can be substitute by the cells taught by claims 1- 39 and 68- 78 to generate a composition comprising population of cells capable of giving rise to CFU-F, that are preadsorbed onto ceramic vehicles and are suitable for implantation . The strongest rationale for combining references is a recognition,

expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 25, 42, 43, 45, 50 and 51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1- 39 and 68- 78 of copending Application No. 10/813747 in view of US Patent 5,591,625.

The teachings of claims 1- 39 and 68- 78 of copending Application No. 10/813747 has been discussed supra.

Claims 1- 39 and 68- 78 of copending Application No. 10/813747do not explicitly recited an enriched cells population wherein said cells are capable of giving rise to CFU-F or a composition comprising said cells wherein said cells has an exogenous nucleic acid transformed in to it, as claimed in claims 42 or 50 or wherein said cells has an exogenous nucleic acid that express a therapeutic agent transformed in to it, as claimed in claims 43 or 51 .

US Patent ' 625 teaches genetically engineered human mesenchymal stem and progenitor cells that have been transformed with exogenous nucleic acid that expresses a therapeutic agent (see entire document, overlapping column 1 and 2 in particular). US Patent' 625 teaches that said cells can be used to treat various diseases including genetic disorders, diseases of bone and cartilage and bone marrow or to be use to release of therapeutics (see column 2, lines 1-65 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '625 to claims 1- 39 and 68- 78 of copending Application No. 10/813747 to obtain a claimed an enriched cells population wherein said cells are capable of giving rise to CFU-F or a composition comprising said cells wherein said cells has an exogenous nucleic acid transformed in to it or wherein said cells has an exogenous nucleic acid that express a therapeutic agent transformed in to it.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because a genetically engineered human mesenchymal stem and progenitor cells that have been transformed with exogenous nucleic acid that expresses a therapeutic agent can be used to treat various diseases including genetic disorders, diseases of bone and cartilage and bone marrow or to be use to release of therapeutics as taught by US Patent '625 . Said cells can be substituted by the cells recited by claims 1- 39 and 68- 78 of copending Application No. 10/813747 since both referenced and recited cells are human mesenchymal progenitor cells that can be used to treat various diseases including genetic disorders, diseases of bone and cartilage and bone marrow. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

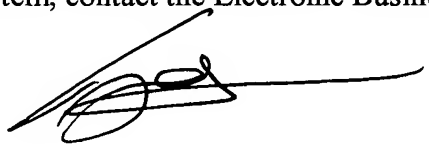
This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
June 13, 2005

Application No.:_____

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE